Anaesthesia for a patient with a cardiac transplant

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Key points

- Liaise with the transplant team
- Donor coronary artery disease is the major long-term complication
- Immunosuppression results in an increased susceptibility to infection and scrupulous aseptic technique is required for any practical procedure
- Ensure that cytomegalovirus-negative recipients receive only cytomegalovirus-negative blood products
- Cardiac denervation alters the pharmacological response to certain drugs

Cardiac transplantation has evolved over the last three decades from a procedure with a 1-year survival of 20% to an established treatment for end-stage heart failure. Between 1991 and 2000, there were 2922 heart transplants performed in the UK. One- and 10-year survivals are currently 90% and 50%, respectively, and 50% of recipients are aged 50 yr or over at the time of transplantation.

Cardiac transplant recipients have an increased requirement for non-cardiac surgery; a quarter of patients undergo surgery within 2 years of transplantation. The anaesthetist may encounter such patients on both elective and emergency theatre lists. In addition, heart transplant patients may suffer medical or surgical complications that necessitate admission to the intensive care unit. Effective anaesthetic care is dependent on knowledge of the complications that occur in these patients, an appreciation of the side-effects of their immunosuppressive therapy and a clear understanding of the changes in physiology and pharmacology that cardiac transplantation produces.

Complications of cardiac transplantation

Donor coronary artery disease

Donor coronary artery disease is the major long-term medical complication and is the commonest cause of death beyond the first year after transplantation. This form of coronary artery disease is immunologically mediated and differs from coronary atherosclerosis in non-transplant patients in that the lesions begin in the microvasculature and involve proximal vessels only when far advanced. Most importantly, presenting symptoms relate to the onset of left ventricular dysfunction or arrhythmia and patients do not present with angina because the heart is denervated. Atheroma may be demonstrated by angiography in 50% of patients 5 yr after transplantation. However, intracoronary ultrasonography has shown intimal thickening in most patients by the end of the first year. Therefore, it is essential that coronary perfusion pressures are maintained during anaesthesia.

Rejection

Acute rejection is an important clinical problem in the first year but is infrequent in longer-term patients on stable immunosuppressive treatment. Routine surveillance cardiac biopsies are performed regularly during the first year and as clinically indicated thereafter. Biopsies are graded using the Billingham classification of mild, moderate, severe and resolving rejection. They are performed via the right internal jugular vein and this site should ideally be avoided when central venous access is required for other purposes. Unexplained weight gain, fluid retention or pyrexia can reflect rejection, as does deterioration in graft function on echocardiography. Endomyocardial biopsy is the gold standard for the diagnosis of rejection.

Immunosuppression

Immunosuppression is usually achieved with triple therapy based on azathioprine, cyclosporin and prednisolone (see below). Long-term treatment with these drugs is associated with infection, increased incidence of malignancy, musculoskeletal problems and chronic renal impairment. Common malignancies include squamous cell carcinoma of the skin and lymphoma. Epstein-Barr virus is an important aetiological factor in post-transplantation lymphoma and a proportion resolve with high dose acyclovir therapy combined with reduced immunosuppression.

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Although cyclosporin has revolutionised cardiac transplantation outcomes, nephrotoxicity is a major problem. Acute nephrotoxicity is reversible but chronic toxicity may lead to end-stage renal disease and dialysis. The presence of renal failure will influence the choice and dose of certain anaesthetic drugs, particularly muscle relaxants.

Associated diseases

It should be remembered that patients may have required transplantation for a systemic disease, the complications of which may have anaesthetic implications. For example, patients who had ischaemic cardiomyopathy are likely to have generalised atherosclerosis. Uncomplicated diabetes is not a contra-indication to transplantation and diabetes may develop *de novo* as a complication of steroid immunosuppression. Transplantation is a recognised treatment for both sarcoid and amyloid cardiomyopathy. Epilepsy is common post-cardiac transplantation and patients may be taking liver enzyme-inducing anticonvulsant therapy. Hypertension is common after cardiac transplantation and may, in part, be related to cyclosporin therapy. Angiotensin converting enzyme inhibitors are a popular treatment for post-transplantation hypertension and can interact with a number of anaesthetic agents to produce intra-operative hypotension.

Elective or emergency surgery may be needed for a range of surgical conditions (*e.g.* incision and drainage of abscesses, repair of inguinal hernias, perforated viscus or gastrectomy for lymphoma). There is also a high incidence of cholelithiasis and pancreatitis necessitating cholecystectomy. In addition, immunosuppression-induced gingival hyperplasia may require dental treatment. A number of cardiac recipients become pregnant and this is associated with a high incidence of pre-eclampsia which may necessitate caesarean section.

Immunosuppressive drugs

Immunosuppression is usually achieved with triple therapy based on azathioprine, cyclosporin and prednisolone. It has been shown to improve survival compared with double therapy (cyclosporin and prednisolone). Doses of the three drugs can be manipulated to obtain adequate immunosuppression while avoiding individual variations in side-effects.

Azathioprine is metabolised by the liver to mercaptopurine and acts non-specifically by inhibition of T- and B-cell clone expansion. Its immunosuppressive action is correlated with its effect on the white cell count. An intravenous form of the drug exists, but this is very irritant and, in practice, the drug is often omitted in patients who are unable to take oral medication. Mycophenolate is an alternative to azathioprine, offering a reduced incidence of acute rejection at the expense of an increased likelihood of opportunistic infection.

Cyclosporin has revolutionised the efficacy of heart transplantation. It was first isolated from yeast and recognised as a potent inhibitor of cellular immunity in the early 1970s. It is non-myelotoxic but markedly nephrotoxic. Cyclosporin is highly lipophilic and has a variable oral bioavailability (at best 30%). Blood cyclosporin concentrations and rejection status guide dosage. Alterations in gastrointestinal function resulting from ileus or abdominal surgery may profoundly decrease cyclosporin absorption and monitoring of concentrations may be required over the peri-operative period. One-third of the oral dose can be given by intravenous infusion over 2–6 h, if necessary. The intravenous preparation contains polyethoxylated castor oil and anaphylaxis has been described. A number of drugs can increase blood cyclosporin concentrations, thus increasing the risk of nephrotoxicity and other side-effects. However, others can reduce blood concentrations, thus increasing the risk of rejection (Table 1). High

Table 1 Cyclosporin drug interactions

Increased cyclosporin concentration	Reduced cyclosporin concentration	Nephrotoxicity	Hyperkalaemia
Grapefruit juice	Rifampicin	Increased risk of nephrotoxicity with NSAIDs	Angiotensin-converting enzyme inhibitors
Amiodarone	St John's wort	Aminoglycosides	Angiotensin-II antagonists
Allopurinol	Anti-epileptics	Co-trimoxazole	Potassium-sparing diuretics
Chloramphenicol		Quinolone antibiotics	
Doxycycline		Amphotericin	
Macrolide antibiotics			
Fluconazole			
Chloroquine			
Calcium antagonists			
Cimetidine			

cyclosporin concentrations can precipitate convulsions. Tacrolimus is an alternative to cyclosporin but it is also associated with side-effects, particularly diabetes.

Prednisolone doses are tapered after transplantation and kept as low as possible to minimise hypertension and other classical steroid side-effects. Intravenous hydrocortisone, at doses higher than equivalent prednisolone maintenance, can be used as a substitute for both prednisolone and azathioprine during periods when oral medication is not possible.

Atypical infections

Immunosuppression renders heart transplant recipients vulnerable to infection, particularly in the initial post-transplantation period when immunosuppressive therapy is most intense. Staphlococcal mediastinitis, re-activation of previous infection with cytomegalovirus (CMV) and *Toxoplasma gondii* are early postoperative complications. In the longer-term recipient, common bacteria can cause infections in unusual places and uncommon organisms may be involved in apparently straightforward infections.

Susceptibility to intracellular bacteria such as *Listeria monocytogenes*, non-typhoid salmonellae and mycobacteria is increased. Primary CMV infection can result in pronounced symptomatic disease and has a predilection for the lung, gastrointestinal tract and retina. CMV seronegative recipients requiring blood transfusion pre-operatively should receive blood from CMV-negative donors. Manifestations of primary toxoplasmosis include encephalitis, myocarditis and pneumonitis. *Pneumocystis carinii* and *Legionella pneumophilia* should be considered in the differential diagnosis of transplant recipients with pneumonia. Invasive aspergillosis may be a terminal event but treatment with liposomal amphotericin can result in a successful outcome. Oesophageal infection with *Candida* or herpes simplex virus presents as dysphagia. It should be remembered that infections caused by *Candida* spp. other than *C. albicans* are often fluconazole resistant.

Accurate microbiological diagnosis should be followed by prompt treatment with an appropriate antibiotic. Empirical therapy is normally reserved for life-threatening infections. Expert microbiological advice should be sought regarding sample collection and antibiotic therapy if infection is suspected.

Physiology and pharmacology

At implantation, the donor atria are sutured to a cuff of recipient atrial tissue. The recipient atrial remnant remains electrically active though this activity is rarely apparent on the surface ECG. Recipient atrial activity does not cross the suture line and donor heart rate is dependent on donor sinus node activity. Surgical disruption of the blood supply to the donor sinus node can result in persistent bradycardia and, together with persistent atrioventricular nodal conduction disturbance, this accounts for the 10% of recipients who require permanent pacemaker implantation. Right bundle branch block occurs in 10% of donor hearts making detection of peri-operative ischaemia from the surface ECG difficult.

The transplanted heart has no autonomic innervation. The resting heart rate is typically 90–100 bpm due to the loss of vagal tone. The normal reflex heart rate changes that occur in response to laryngoscopy, visceral traction or fluctuations in blood pressure are lost. The lack of rapid homeostatic adjustments in heart rate to sudden drug-induced changes in vascular resistance can produce wide swings in blood pressure which can be troublesome during anaesthesia. Therefore, an adequate preload must be maintained. The heart rate response to exercise and other physiological stresses is also altered. From the initially higher resting heart rate, a blunted response to exercise is seen with a gradual rise to a reduced maximum heart rate and then a gradual decline in heart rate following the

Table 2 Pharmacology after cardiac transplantation

Drug	Effect in recipient	Mechanism
Adenosine	4-fold increase in sinus and atrioventricular nodal blocking effect	Denervation supersensitivity
Digoxin	Minimal delay in atrioventricular nodal conduction	Denervation
Atropine	No effect on heart rate	Denervation
Epinephrine	Increased contractility and chronotropy	Denervation supersensitivity
Norepinephrine	Increased contractility and chronotropy	Denervation supersensitivity
Isoprenaline	Normal chronotropic effect	
Glyceryl trinitrate	No reflex tachycardia	Baroreflex disruption
Pancuronium	No tachycardia	Denervation
Succinylcholine	No bradycardia	Denervation
Neostigmine	No bradycardia	Denervation

cessation of exercise. This reflects a dependence on endogenous circulating catecholamines in order to mount a chronotropic response rather than the normal mechanism of vagal withdrawal together with an increase in cardiac sympathetic nerve activity. Changes in heart rate cease to be an indicator of the depth of anaesthesia.

Denervation also alters the pharmacological response to certain drugs. The cardiac vagolytic effect of drugs such as atropine and glycopyrrolate are lost and denervation supersensitivity to other drugs is seen (Table 2). Digoxin controls the ventricular response rate in atrial fibrillation by increasing vagal tone and, therefore, ceases to be effective as an anti-arrhythmic in the transplanted heart. Marked sensitivity to adenosine is seen and a starting dose of 1 mg rather than 3 mg should be employed if this drug is used to terminate re-entrant tachycardia involving the atrioventricular node.

Arrhythmias are common in the initial weeks after transplantation, but decline in frequency thereafter. Increasing episodes of arrhythmia may be a reflection of rejection, although this finding is neither sensitive nor specific. The Starling pressure–volume relationship remains intact and contributes to increased demands for cardiac output emphasising the importance of ensuring an adequate preload prior to induction of anaesthesia. Limited sympathetic re-innervation is described and some long-term recipients may experience anginal pain.

Pre-operative assessment

All heart transplant recipients are enrolled in a follow-up programme and recent information with respect to graft function (echocardiography), rejection status (endomyocardial biopsy), coronary disease (surveillance angiography) and CMV status should be obtained from the transplant co-ordinator. Advice should also be sought regarding the peri-operative management of immunosuppressive therapy which may need to be given intravenously. Exercise tolerance and the presence or absence of orthopnoea should be ascertained. Pre-operative investigations should be determined by the condition of the patient and the proposed procedure but electrolyte estimation to ensure normokalaemia must be done. Current information regarding antibiotic prophylaxis should be sought from the microbiologist or transplant team.

Conduct of anaesthesia

As with any anaesthetic, the choice of technique is largely based on the patient's general health and type of procedure being performed. For instance, spontaneous respiration via a laryngeal mask would be suitable for an elective inguinal hernia repair. There is no contra-indication to regional techniques but a strict aseptic technique is essential. Minimal standards of monitoring in accordance with the recognised guidelines should be used. Invasive methods of monitoring should be used as indicated but scrupulous asepsis should be followed and the lines removed as soon as possible after the procedure.

The anaesthetist should aim for normovolaemia prior to induction because of the dependence of cardiac output on preload. In the seriously ill patient, insertion of a pulmonary artery flotation catheter to measure preload may be considered necessary but this is contra-indicated in the presence of a permanent pacemaker. Alternatively, intra-operative transoesophageal echocardiography can provide accurate information regarding preload and myocardial contractility without the need for an invasive vascular procedure.

Oral tracheal intubation is preferred over nasal intubation due to the possibility of infection caused by dissemination of nasal flora. The use of breathing system filters and either a disposable laryngoscope blade or laryngoscope blade sheath are sensible precautions. The muscle relaxant cis-atracurium offers good cardiovascular stability and does not accumulate in the presence of renal failure. Scrupulous asepsis should be used for vascular and urinary catheter insertion. Hypotension occurring at any time should be rapidly corrected to ensure adequate coronary perfusion. This depends on the presence of an adequate preload and the judicial use of vasoconstrictors such as phenylephrine or metaraminol. Direct acting chronotropic agents such as ephedrine and isoprenaline should be available, as should an external pacemaker device if the patient is pacemaker-dependent. Steroid-induced osteoporosis or skin fragility mandates careful handling and positioning of the patient.

Postoperative care

During the postoperative period, further liaison with the transplant team may be necessary for advice regarding the management of immunosuppression and antibiotic therapy, especially if the patient is to remain nil-by-mouth. Normal regimens for postoperative analgesia should be followed but the use of non-steroidal anti-inflammatory drugs for postoperative analgesia is best avoided in the presence of renal impairment. Local anaesthetic blocks may be useful to ensure adequate postoperative analgesia. Intravascular lines, drains, endotracheal tubes and catheters should be removed as soon as possible to reduce the risk of infection.

Conclusions

Remember that these patients have already undergone extensive hospital treatment and many know a lot about their own problems. They are also well-known to the transplant team. There is an on-call co-ordinator for cardiac transplant patients who can give advice about the long-term medical problems of every patient and what to do about maintaining immunosuppression peri-operatively. Keep the anaesthetic technique as simple as possible and always maintain the preload. These patients do not respond to atropine but require direct acting sympathomimetic agents such as isoprenaline or epinephrine to increase heart rate.

Key references

Borow KM, Neumann A, Arensman FW, Yacoub MH. Cardiac and peripheral vascular responses to adrenoceptor stimulation and blockade after cardiac transplantation. *J Am Coll Cardiol* 1989; **14**: 1229–38

Hosenpud JD, Cobanoglu A, Norman DJ, Starr A. (eds) *Cardiac Transplantation – A Manual for Health Care Professionals*. New York: Springer, 1990

Sharpe MD. Anaesthesia and the transplanted patient. *Can J Anaesth* 1996; **43**: R89–93

Wilson RF, Christensen BV, Olivari MT, Simon A, White CW, Laxson DD. Evidence for structural sympathetic reinnervation after orthotopic cardiac transplantation in humans. *Circulation* 1991; **83**: 1210–20

See multiple choice questions 50–53.